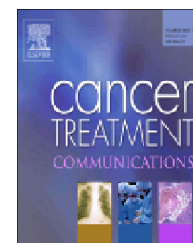


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Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin

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Received 8 September 2014; accepted 5 November 2014

KEYWORDS

Pancytopenia;
Metastatic breast cancer;
Doxorubicin;
Continuous

Abstract

Complete bone marrow infiltration with profound pancytopenia is very uncommon in breast cancer. Bone marrow metastasis can frequently occur following development of metastatic breast cancer. However, bone marrow failure as the herald of this disease is not typically seen. Very limited data exists as to the safest and most efficacious manner to treat patients with profound pancytopenia due to metastatic solid tumor involvement. In this case, the patient's thrombocytopenia was particularly worrisome, requiring daily platelet transfusions. There was also concern that cytotoxic chemotherapy would exacerbate the patient's thrombocytopenia and increase bleeding risk. The patient's dramatic response to chemotherapy with full platelet recovery is also highly unusual. For our patient, continuous doxorubicin successfully "unpacked" the bone marrow despite a low baseline platelet level, and without increasing the need for more frequent platelet transfusion or risk of catastrophic bleeding. Given the rarity of this presentation, it is currently unknown if the majority of similar patients experience near full recovery of hematopoietic function after initiation of appropriate systemic treatment for metastatic disease.

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1. Introduction

Breast cancer is the most common malignancy in women and number one cause of death in women between the ages

of 45 and 55 in the United States [1]. Although metastatic disease, considered incurable, is rarely seen at the time of initial diagnosis, approximately 20% of women with operable breast cancer eventually relapse, with about 70% of the relapses as distant metastases [2-5]. Approximately 80% of women with metastatic breast cancer have skeletal metastases, which are often the result of bone marrow infiltration of malignant cells with subsequent progression and invasion of the skeletal cortex [6-9]. The most common complications of skeletal metastases are pathologic fractures, spinal cord compression as the result of vertebral compression fracture or extension of the tumor beyond the epidural space, and hypercalcemia [7-9]. Furthermore, skeletal metastases sometimes require surgery or radiation therapy to treat pain or an impending fracture. Bone marrow metastases result in the invasion and destruction of the bone tissue matrix by tumor cells [6]. Although bone marrow infiltration by metastases is commonly present among breast cancer patients, total bone marrow infiltration resulting in profound pancytopenia is extremely rare [6,10].

2. Case report

A 62 year-old female presented with increased fatigue that was interfering with her activities of daily living. Her previous medical history was remarkable only for hypertension. Her family history included lung cancer in her mother. On physical exam, she was ill-appearing and fatigued. Sclera were anicteric. Lips were dry and oral mucosa was notable for blood tinged secretions. Lungs were clear to auscultation bilaterally. Cardiovascular exam was normal, with no murmurs, rubs or gallops appreciated. Abdomen was soft and nontender without organomegaly. Her breast exam was

notable for a fixed, 1 cm left axillary lymph node. Neither breast had a palpable mass or skin changes. Peripheral blood laboratory tests indicated severe pancytopenia. Her white blood cell (WBC) count was 3.2 K/ μ L, hemoglobin (Hgb) was 6.8 g/dL, and platelet count was 3 K/ μ L. Multiple imaging studies, including computed tomography (CT) of the chest, abdomen and pelvis, as well as a bone scintigraphy were completed as part of the initial diagnostic work up. Chest CT revealed left axillary adenopathy and a medial, nodular left breast lesion. The bone scintigraphy scan showed diffuse skeletal metastatic disease involving multiple vertebrae and the pelvis. A mammogram had also been performed and showed an irregular spiculated nodule in the upper inner left breast. The patient subsequently underwent a core needle biopsy of an enlarged left axillary lymph node. The biopsy revealed a metastatic lobular carcinoma strongly positive for both estrogen and progesterone receptors (ER and PR) and negative for HER2 and E-cadherin by immunohistochemical staining.

To further evaluate the patient's profound pancytopenia, which required frequent transfusion of packed red blood cells (pRBC) and platelets, the patient underwent a bone marrow biopsy. The pathology showed that the metastatic carcinoma had entirely replaced the bone marrow (Figure 1). The tumor cells were positive by immunohistochemical staining for cytokeratin AE1/AE3, ER and PR, but were negative for HER2, consistent with metastatic breast cancer.

After much discussion of the risks and benefits of therapy in view of profound pancytopenia, the patient initiated systemic therapy with doxorubicin administered as a continuous three day infusion (20 mg/m²/day) on a 21 day cycle in the inpatient setting. A continuous infusion of doxorubicin was selected based on small, prior studies suggesting that acute and chronic toxicities, including bone marrow suppression, may be lessened when doxorubicin is administered as a continuous versus bolus

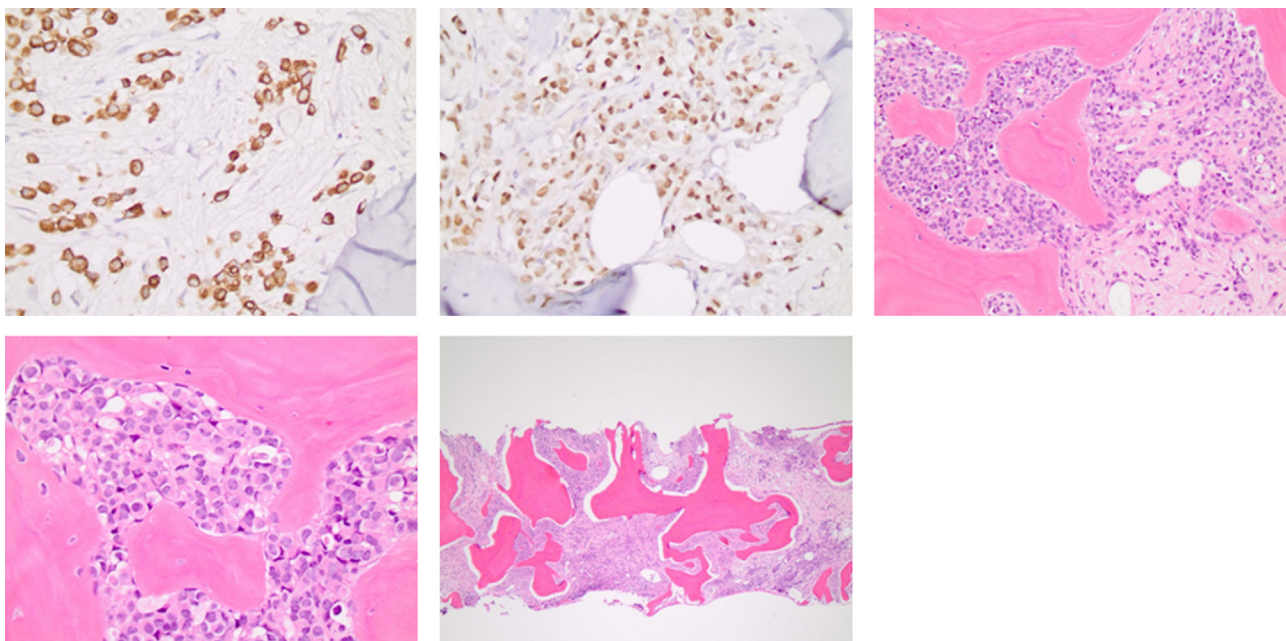


Figure 1 The bone marrow biopsy shows that the hematopoietic elements are entirely replaced by fibrosis and metastatic carcinoma infiltrating individually and in small clusters, and comprised of intermediate sized cells with round to ovoid nuclei, a thin rim of cytoplasm and occasional intracytoplasmic vacuoles.

infusion [11–13]. The patient ultimately received 3 cycles of this therapy. During the first cycle, the doxorubicin dose was reduced by 50% due to increased transaminases that normalized with subsequent cycles of therapy. The second cycle was given at full dose, but was complicated by febrile neutropenia requiring hospitalization. The doxorubicin dose was therefore reduced by 25% during the third cycle. After 3 cycles of therapy, continuous doxorubicin was switched to monthly liposomal doxorubicin (40 mg/m^2) for ease of administration in the outpatient setting since the patient's platelets had sufficiently recovered. As shown in Figure 2, the patient's pancytopenia steadily improved after initiation of chemotherapy. Approximately four months after commencing treatment, her WBC rose to $5.4 \text{ K}/\mu\text{L}$, Hgb increased to 11.6 g/dL and platelet count improved to $131 \text{ K}/\mu\text{L}$. Approximately thirteen months after beginning the treatment, the patient experienced a near full recovery from her pancytopenia with no evidence of anemia or thrombocytopenia. Her laboratory tests showed WBC of $4.8 \text{ K}/\mu\text{L}$, RBC of $4.00 \text{ M}/\mu\text{L}$, Hgb of 12.8 g/dL and platelet count of $160 \text{ K}/\mu\text{L}$ at that time, indicating a remarkable response to treatment (Figure 2). After four cycles of liposomal doxorubicin, the patient was transitioned to endocrine therapy with an aromatase inhibitor, letrozole.

Her laboratory profile remained stable 43 months after initiation of continuous doxorubicin. In her last 12 months of life, her disease progressed in the liver, bone, orbit and brain. She was treated with radiation to the orbital metastasis and brain metastases, but declined further systemic chemotherapy. In her last month of life, her platelets dropped to 15 with normal white blood count and hemoglobin levels. She ultimately died from complications of metastatic breast cancer 44 months after her initial diagnosis.

3. Discussion

Complete bone marrow infiltration with profound pancytopenia is very uncommon in breast cancer. Bone marrow metastasis can frequently occur following development of metastatic breast cancer [14]. However, bone marrow failure as the herald of this disease is not typically seen. Very limited data exists as to the safest and most efficacious manner to treat patients with profound pancytopenia due to metastatic solid tumor involvement.

In this case, the patient's thrombocytopenia was particularly worrisome, requiring daily platelet transfusions. There was also concern that cytotoxic chemotherapy would exacerbate the patient's thrombocytopenia and increase bleeding risk. The patient's dramatic response to chemotherapy with full platelet recovery is also highly unusual. For our patient, continuous doxorubicin successfully "unpacked" the bone marrow despite a low baseline platelet level, and without increasing the need for more frequent platelet transfusion or risk of catastrophic bleeding. Given the rarity of this presentation, it is currently unknown if the majority of similar patients experience near full recovery of hematopoietic function after initiation of appropriate systemic treatment for metastatic disease.

Pancytopenia is not a common presentation in patients with metastatic breast cancer. In several studies, pancytopenia was noted as the consequence of adjuvant chemotherapy with alkylating agents and topoisomerase II inhibitors rather than metastatic disease [15]. Some have suggested that the use of growth factor support such as filgrastim or peg-filgrastim may also contribute to the risk of developing pancytopenia related to myelodysplastic syndrome or acute myeloid leukemia, although that association has not been completely established [16]. Saito et al. reported on a metastatic breast cancer patient with pancytopenia who had evidence of concurrent therapy-related acute myeloid leukemia and bone marrow metastasis [17].

In our case, bone marrow infiltration with metastatic breast cancer was the primary cause of pancytopenia. This has rarely been described in the literature and includes both patients with both positive and negative outcomes from therapy. Several reports highlight patients who have responded to systemic therapy including low dose capecitabine, endocrine therapy and trastuzumab monotherapy [28–32]. As expected not all patients respond to therapy. Sasada et al. reported on a case of a patient with bone marrow metastasis from breast cancer [18]. The patient developed pancytopenia with disseminated intravascular coagulation (DIC) and was given weekly paclitaxel therapy with blood transfusion and G-CSF injections. Therapy was

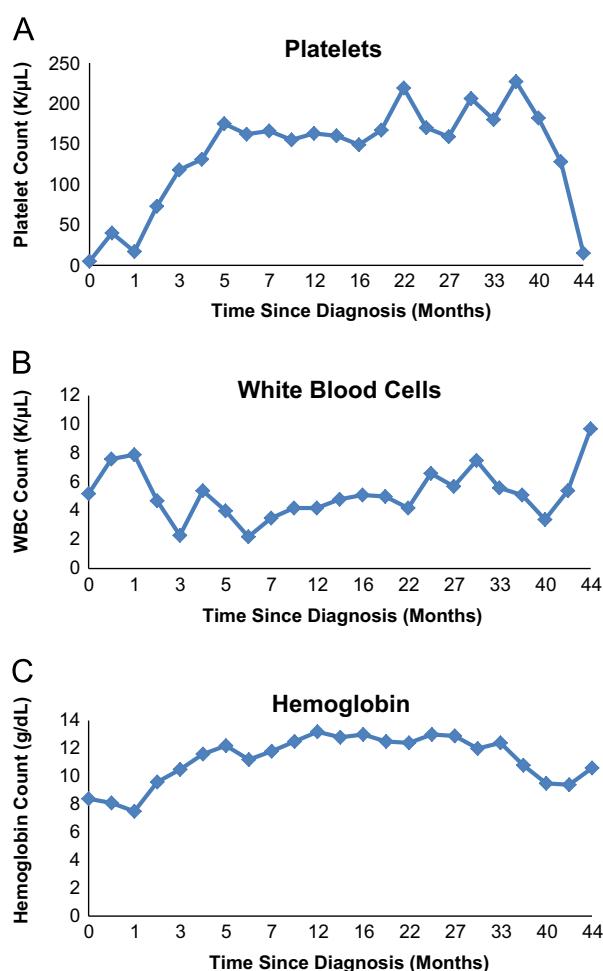


Figure 2 Patient's platelet (A), white blood cell (B) and hemoglobin (C) levels throughout treatment highlighting hematopoietic recovery after continuous doxorubicin therapy.

ineffective and the patient died of gastrointestinal hemorrhage due to complications of pancytopenia that were likely caused by DIC and metastatic disease [18]. Our patient experienced similar bone marrow metastasis and pancytopenia, but was able to achieve sustained disease control through doxorubicin chemotherapy followed by aromatase inhibitor therapy, without bleeding complications. In addition, laboratory tests at the time of diagnosis did not show any evidence of DIC in our case.

In addition to continuous doxorubicin, our patient received zoledronic acid as a part of management of osseous metastasis from breast cancer. Many studies have focused on the prevention of breast cancer due to subclinical bone marrow metastasis caused by dormant disseminated tumor cells (DTCs) in the bone marrow [19-21]. Although DTCs appear to be associated with a higher risk of distant recurrence, they are not known to cause abnormalities in peripheral blood laboratory tests. Solomayer et al. demonstrated the impact of zoledronic acid on DTCs in primary breast cancer patients [22]. The authors found that DTC-positive patients treated with zoledronic acid were more likely to become DTC-negative following a 12 month treatment interval and concluded that treatment with zoledronic acid improved the elimination of DTCs [22]. The role of bisphosphonates in preventing skeletal metastases in patients with high risk early stage breast cancer is controversial [20,23-27]. The contribution of zoledronic acid in bone marrow recovery in this instance is not known.

4. Conclusion

Breast cancer has a tendency to metastasize to the bone marrow, but does not commonly cause bone marrow failure. The case presented describes a patient who developed complete bone marrow infiltration by estrogen receptor positive metastatic breast cancer that led to transfusion dependent pancytopenia. The patient received treatment with continuous doxorubicin and zoledronic acid followed by endocrine therapy, which resulted in complete recovery of normal bone marrow function for 3 years. Drug therapy is a consideration in patients with bone marrow infiltration with good performance status.

Conflict of interest statement

None declared.

Acknowledgments

MBL and RW were supported by NIH K12 training grants.

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